PARAMETER ESTIMATION OF MICROBIAL MODELS USING HYBRID OPTIMIZATION METHODS

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To my beloved wife, children, family, and friends…

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ABSTRACT

Development of biological models is essential as it represents and predicts complex processes within microbial cells. These models are formed by mathematical formulations that depend heavily on a set of parameters whose accuracy is often influenced by noisy and incomplete experimental data. This study is aimed to design and develop new optimization methods that can effectively estimate these parameters by iteratively fitting the model outputs to the experimental data. To achieve this goal, two new hybrid optimization methods based on the Firefly Algorithm (FA) method are proposed. Firstly, a method using evolutionary operations from Differential Evolution (DE) method was developed to improve the estimation accuracy of the parameters. Then, a second method using Chemical Reaction Optimization (CRO) method was proposed to surmount the convergence speed problem during parameter estimation. The effectiveness of the proposed methods was evaluated using synthetic transcriptional oscillator and extracellular protease production models. Computational experiments showed that these methods were able to estimate plausible parameters which produced model outputs that closely fitted in the experimental data. Statistical validation confirmed that these methods are competent at estimating the identifiable parameters. These findings are crucial to ensure that the estimated parameters can generate predictive and sensitive model outputs. In conclusion, this study has presented new hybrid optimization methods, capable of estimating the model parameters effectively whilst taking into account noisy and incomplete experimental data.

ABSTRAK

Pembangunan model biologi adalah penting kerana ia mewakili dan meramalkan proses-proses kompleks di dalam sel-sel mikrob. Model-model ini dibentuk dengan ungkapan matematik yang sangat bergantung kepada satu set parameter yang ketepatannya sering dipengaruhi oleh data eksperimen yang hingar dan tidak lengkap. Kajian ini bertujuan untuk merekabentuk dan membangunkan kaedah-kaedah pengoptimuman yang mampu menganggarkan parameter-parameter ini dengan memadankan ouput model kepada data eksperimen secara berlelaran. Untuk mencapai tujuan ini, dua kaedah pengoptimuman hibrid berasaskan Algorithma Kunang-Kunang telah dicadangkan. Pertama, kaedah yang menggunakan operasi-operasi evolusi daripada kaedah Evolusi Perbezaan telah dibangunkan untuk membaiki ketepatan padanan parameter-parameter. Kemudian, kaedah kedua menggunakan kaedah Pengoptimuman Tindakbalas Kimia telah dicadangkan untuk mengatasi masalah kepantasan penumpuan semasa menganggarkan parameter. Keberkesanan kaedah-kaedah yang dicadangkan telah dinilai menggunakan model pengayun transkripsi sintetik dan model pengeluaran protease luar sel. Eksperimen-eksperimen komputeran menunjukkan kaedah-kaedah ini mampu menganggarkan parameter-parameter yang dapat menghasilkan model output yang hampir padan dengan data eksperimen. Pengesahsahihan statistikal mengesahkan bahawa kaedah-kaedah ini adalah memuaskan dalam menganggarkan parameter-parameter yang dapat dikenalpasti. Penemuan-penemuan ini adalah penting untuk memastikan parameter-parameter yang dianggarkan dapat menjana model output yang boleh diramal dan peka. Kesimpulannya, kajian ini telah mempersembahkan kaedah-kaedah pengoptimuman hibrid yang baru, yang mampu menganggarkan parameter-parameter model secara efektif dengan mengambilkira data eksperimen yang hingar dan tidak lengkap.

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LIST OF ABBREVIATION

ABC	-	Artificial Bee Colony
ACO	-	Ant Colony Optimization
AIC	-	Aikake Information Criterion
AIS	-	Artificial Immune System
AMP	-	Adenosine Monophosphate
AS	-	Atorvastatin
ASL	-	Lipophilic Lactone
ASLpOH	-	Para-Hydroxy-Atorvastatin Lactone Acid
ATP	-	Adenosine Triphosphate
BA	-	Bee Algorithm
BFGS	-	Broyden–Fletcher–Goldfarb–Shanno
CPU	-	Central Processing Unit
CRO	-	Chemical Reaction Optimization
CSA	-	Clonal Selection Algorithm
DE	-	Differential Evolution
DEBCO	-	Differential Evolution Bee Colony Optimization
DNA	-	Deoxyribonucleic Acid
EA	-	Evolutionary Algorithm
ES	-	Evolution Strategy
EKF	-	Extended Kalman Filter
FA	-	Firefly Algorithm
FIM	-	Fisher’s Information Matrix
FGF	-	Fibroblast Growth Factor
GA	-	Genetic Algorithms
HIV	-	Human Immunodeficiency Virus
KEGG	-	Kyoto Encyclopedia Of Genes And Genomes
LPS	-	Lipopolysaccharide

mRNA	-	Messenger Ribonucleic Acid
NEFA	-	New Evolutionary Firefly Algorithm
NFL	-	No Free Lunch
NLP	-	Nonlinear Programming
ODEs	-	Ordinary Differential Equations
OS	-	Operating System
PCR	-	Polymerase Chain Reaction
PSM	-	Presomitic Mesoderm
PSEO	-	Particle Swarm Evolutionary Optimization
PSO	-	Particle Swarm Optimization
RA	-	Retinoic Acid
RNA	-	Ribonucleic Acid
SBFA	-	Selective Breeding Firefly Algorithm
SBML	-	Systems Biology Markup Language
S-CRO	-	Swarm-Based Chemical Reaction Optimization
SQP	-	Sequential Quadratic Programming
SRES	-	Stochastic Ranking Evolutionary Strategy
SS	-	Scatter Search

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CHAPTER 1

INTRODUCTION

1.1 Problem Background

Computational systems biology is aimed to elucidate complex behaviours of biochemical reactions within cells through computational approaches (Sun *et al*., 2012; Lages *et al*., 2012). This field of research is important to acquire better understanding of how these reactions work as a system (Karr *et al*., 2012; Isalan, 2012). In general, these reactions can be represented by using computational models. These models are constructed based on mathematical formulations such as ordinary differential equations (ODEs) to quantify the changes of specific biochemical concentrations over a sample of observation time. The development of these models commonly involves two major stages, namely network structure identification and parameter estimation (Tashkova *et al*., 2011; Chou and Voit, 2009). On the network structure identification stage, the structures of the models are formed by modelling experts. This often requires prior knowledge of the reaction networks. On the other hand, the parameter estimation stage is performed to determine parameter values in the constructed models. These parameters are usually approximated based on the available experimental data obtained from the high-throughput experiments. This is a challenging task because the biochemical reactions in the systems are highly nonlinear and the experimental data are frequently noisy and incomplete (Tashkova *et al*., 2011; Sun *et al*., 2012; Lages *et al*., 2012).

The purpose of the parameter estimation stage is to equip the models with a plausible set of parameters. These parameters are used to produce model outputs

that are consistent with the experimental data. Thus, these parameters are crucial to signify physical properties of the systems, such as kinetic constants and reaction rates. However, these parameters are difficult to be extracted from the high-throughput experiments. In most cases, these parameters are estimated using nonlinear programming (NLP) methods (Balsa-Canto *et al*., 2012; Sun *et al*., 2012).

The parameter estimation task is considered as an optimization problem, in which optimal model parameters are repeatedly determined by the difference between the model outputs and the corresponding experimental data is minimized. Generally, there are two major approaches for this task: gradient and stochastic searching strategies (Chou and Voit, 2009). The gradient searching strategy usually utilizes local search algorithms to find the parameters based on the initial guesses of the state measurements. However, due to the complexity of the biological systems, it is difficult to determine these initial guesses as the values are often unknown. Moreover, the nonlinearity of the models may lead the searching to least substantial parameters (Balsa-Canto *et al*., 2011). To overcome this limitation, stochastic searching strategy is applied. This strategy employs global optimization methods that initiate the searching processes with a set of randomly selected model parameters. Nevertheless, a major drawback of this strategy is the high computational cost. Furthermore, the strategy sometimes has difficulty to converge the searching to the local optimum solutions (Sun *et al*., 2012).

To surmount these bottlenecks, many researches have considered the use of hybrid optimization methods. In these methods, the convergence performance of the stochastic searching strategy is improved by incorporating other optimization algorithms (Rodriguez-Fernandez *et al*., 2008; Ashyraliyev *et al*., 2009). In recent years, the hybrid optimization methods have shown potential achievements in estimating parameters of the biological models (Lages *et al*., 2012; Sun *et al*., 2012; Tashkova *et al*., 2011). Moreover, Evolutionary Algorithms (EAs) such as Differential Evolution (DE) (Storn and Price, 1997), Clonal Selection Algorithm (CSA) (De Castro and Von Zuben, 2002), and Chemical Reaction Optimization Algorithm (CRO) (Lam and Li, 2010) have presented promising capabilities in handling measurement noise and incompleteness of the experimental data (Sun *et al*., 2012; Abdullah *et al*., 2011). This is due to the fact that these algorithms employ random recombination searching approaches that utilize neighbouring

vectors within the population of solutions. Therefore, incorporating EAs may facilitate improvements of stochastic searching strategy, especially in terms of robustness over noisy and incomplete experimental data during the estimation process (Tashkova *et al*., 2011).

Besides handling measurement noise and incompleteness of the experimental data, another challenge may also arise in the parameter estimation task, namely parameter non-identifiability. The parameter non-identifiability occurred when the estimated parameters fail to produce distinctive model outputs. There are two types of parameter non-identifiability, namely structural and practical non-identifiability (Balsa-Canto and Banga, 2010). The structural non-identifiability generally occurred due to limitations in the model structure, in which can be solved by modifying the models until the model outputs are consistent with the experimental data (Bandara *et al*., 2009). On the other hand, practical non-identifiability problem is much complicated as it often occurs due to the quality and amount of the experimental data (Chis *et al*., 2011).

Providing sufficient experimental data and constraints may be useful to solve this problem. This may allow the parameter estimation task to find unique parameters based on the experimental data (Balsa-Canto and Banga, 2010). Finding identifiable parameters is useful for model selection. Model selection is generally defined as the capability to choose plausible models based on the given experimental data. Therefore, unique parameters that are estimated by the optimization methods may produce distinctive model outputs, in which will facilitate to differentiation of models (Miao *et al*., 2009; Lillacci and Khammash, 2010). The model selection permits further analyses of the model structures according to the available experimental data, especially for finding new pathways to improve certain biochemical productions.

1.2 Problem Statement

Computational systems biology has become an increasingly important research area in the recent years (Sun *et al*., 2012; Lages *et al*., 2012). This field of research is aimed to gain better understanding of how complex biological process response as a system within living cells. This is often facilitated using computational models (Sun *et al*., 2012; Tashkova *et al*., 2011; Chou and Voit, 2009). These models commonly contain a set of parameters that represent the physiological properties of the systems. Generally, obtaining these parameters is a challenging task. In recent years, many optimization methods have been proposed to estimate these parameters by fitting the model outputs with the corresponding experimental data. This is usually performed by minimizing the difference between these two data. However, the available experimental data are usually incomplete and has measurement noise. Thus, designing and developing robust optimization methods are crucial to ensure the accuracy of the estimation. Moreover, the estimated parameters are sometime non-identifiable, which thwart the possibility of finding plausible parameters that may produce informative model outputs. As the reliable parameters are difficult to be attained, this may lead to further difficulty in selecting feasible models based on the given experimental data.

Currently, there is an increasing number of nonlinear optimization methods proposed to estimate the parameters in the biological models (Sun *et al*., 2012; Balsa-Canto *et al*., 2012; Tashkova *et al*., 2011). The aim of these methods is to find the optimal parameter set which may produce the model outputs that closely fit the corresponding experimental data. Conventionally, derivative-based optimization methods are utilized, including maximum likelihood (Lloyd-Smith, 2007) and gradient descent (Ashyraliyev *et al.*, 2008) methods. More recently, a local optimization method, namely Extended Kalman Filter (EFK) (Costa, 1994) method, is employed (Sun *et al*., 2008). Lillacci and Khammash (2010) introduced an improved EFK method that incorporates the continuous model outputs and the experimental measurements to estimate the parameters using state space searching approach. Additionally, Zheng and co-workers (2012) proposed inequality constraints to improve the estimation by the EFK method. However, both improved methods commonly require the use of model refinement phases to avoid the searching processes from being trapped into suboptimal solutions. Furthermore, these methods need to consider the limitations of the EFK method that heavily rely

on a good set of initial values for both states and parameters in the models (Sun *et al*., 2008).

In contrast, several previous works have presented prospective achievements by using metaheuristics methods (Balsa-Canto *et al*., 2012). Methods such as Particle Swarm Optimization (PSO) (Kennedy and Eberhart, 1995) and Genetic Algorithm (GA) (Goldberg, 1988) were also used to estimate the parameters in biological systems, which showed promising results (Besozzi *et al*., 2008; Tutkun, 2009). More recently, evolutionary-based metaheuristics methods have received the remarkable attentions (Sun *et al*., 2012; Tashkova *et al*., 2011; Buhry *et al*., 2011). Generally, these methods utilize evolutionary operations such as crossover, mutation, and selection operations to exploit the information of the solutions in the population. Tashkova and co-workers (2011) suggested that the use of DE method is more practical compared to the existing meta-heuristic methods. However, it was also presented that the method may use a substantial amount of computational cost to obtain the best solution (Sun *et al*., 2012; Abdullah *et al*., 2011). Moreover, there is no guarantee that these methods will converge to the global optimum solutions (Balsa-Canto *et al*., 2012). These generally lead to the use of hybrid optimization methods that combine several searching techniques of different metaheuristics methods to overcome these limitations.

Therefore, the problem of this research can be formulated as follows: given the noisy and incomplete experimental data, it is a challenging task to design and develop an effective hybrid optimization method that robustly estimate the model parameters within an acceptable amount of computational time. The proposed method also needs to consider the non-identifiability of the estimated parameters.

1.3 Research Goal and Objectives

The goal of this research is to propose a new hybrid optimization method for estimating model parameters based on noisy and incomplete experimental data. In order to achieve this goal, the following objectives are required to be met:

1. To design and develop a new hybrid optimization method that can handle noisy and incomplete experimental data during the parameter estimation;
2. To evaluate the effectiveness of the proposed method in dealing with practically non-identifiable parameters;

1.4 Research Scopes and Significance

In this research, the metabolic systems of well-studied bacteria are used to evaluate the effectiveness of the proposed optimization methods. The systems, which are formed by a series of biochemical reactions, are used to observe the concentration changes of certain biochemical compounds in specific biological processes. The models used for the parameter estimation problem and non-identifiability analysis is obtained from Biomodels database (Le Novere *et al*., 2006). The models are in the form of Systems Biology Markup Language (SBML) file format. The file contains the information of involved metabolites, reaction rates, parameters and the initial concentration volume used in the high-throughput experiments. The model is simulated using general purpose modelling software, COPASI (Hoops *et al*., 2006). The experimental data for this model is generated *in silico*. This is performed by adding the Gaussian noise into the model outputs to simulate the measurement noise (Lillacci and Khammash, 2010).

The significance of the research is addressed as follows. Firstly, the design and development of new hybrid optimization methods is valuable in term of the computational contribution. The methods utilize the advantages of the evolutionary operations employed by DE and CRO methods to enhance the searching capability of the Firefly Algorithm (FA) method (Yang, 2009) and reduce computational time

significantly. In addition, the methods are capable to handle noisy and incomplete experimental data during the parameter estimation process. Secondly, the outcomes of this research can benefit the systems biology community. This is due to the contribution of the new approach to parameter estimation and non-identifiability analysis. As the optimization methods are robust to measurement noise and incompleteness, this provides effective tools to implement the methods for diverse parameter estimation problems of other biological models.

1.5 Thesis Outline

The organization of the thesis is outlined as follows:

- Chapter 1: This chapter provides the introduction of the research, which encompasses research background, problem statement, goal, objectives, scope and significance of the study.
- Chapter 2: This chapter provides the literature review of the research. The chapter starts with the overview of the bacterial cell. Then, the biological model development is described. This leads to the use of optimization methods for parameter estimation and discussion of related issues on the problem.
- Chapter 3: This chapter provides the research methodology. This chapter presents the research operational framework, description of the data used and an overview of the evaluation measurement.
- Chapter 4: This chapter presents an empirical analysis of the existing optimization methods, ranging from three categories: local, global, and hybrid optimization methods. The methods used in this analysis are Nelder-Mead, Levenberg-Marquardt, PSO, DE, FA, CRO, and two recently proposed hybrid optimization methods, namely Particle Swarm Evolutionary Optimization (PSEO) (Abdullah *et al*., 2013a) and Differential Evolutionary Bee Colony Optimization (DEBCO) (Abdullah *et al*., 2013b) methods. The effectiveness of this method is evaluated using two biological models: synthetic transcriptional oscillators (Kim and Winfree, 2011), and an extracellular protease production (Veening *et al*., 2008) models.

- Chapter 5: In this chapter, a new hybrid optimization method based on FA and CRO methods is proposed. The method is validated for parameter estimation accuracy and its capability on handling non-identifiable parameters.
- Chapter 6: In this chapter, an improved hybrid optimization method based on FA and CRO methods is proposed. This method is aimed to overcome limitations of the method proposed in the previous chapter.
- Chapter 7: This chapter discusses the contribution of the works and future plans to fulfil the research objectives.

1.6 Summary

In this chapter, the introduction of the research is presented. Firstly, the background of the research is discussed. This includes the designing of models for synthetic biology, current parameter estimation methods and challenges of parameter estimation of biological models. Then, the problem statement of the research is addressed. Next, the research goal and objectives are described. Later, the research scopes and the significance of the study are discussed. In the next chapter, the literature review of this research is presented.

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